

## Diffusion Tensor Imaging of Leukoaraiosis, Normal Appearing Brain Tissue, and Normal Brain Tissue

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### ABSTRACT

Diffusion Tensor Imaging (DTI) is an advanced magnetic resonance imaging (MRI) technique. DTI provides quantitative information at microstructural level via its parameter indices e.g. mean diffusivity (MD) and fractional anisotropy (FA). It also allows for visualization of neuron fibres through a specific technique called fibre tractography. Leukoaraiosis is an asymptomatic pathological condition of the brain white matter which appears hyperintense on T2-weighted MRI images. Association of leukoaraiosis with age and ischemic heart disease have been previously reported. The objective of this study is to compare MD and FA values measured in various areas of the brain white matter (WM), grey matter (GM), and cerebrospinal fluid (CSF) in humans using DTI. 30 subjects with leukoaraiosis and 12 subjects without leukoaraiosis underwent brain scan using GE 1.5 Tesla MRI system. Region of interests were located in the CSF and various WM and GM areas. Comparison of MD and FA values was made between leukoaraiosis tissue (LA) and normal appearing brain tissue (NABT) measured within the same leukoaraiosis subjects, and with normal brain tissue (CONTROL) of healthy control subjects. LA demonstrated a significantly higher MD and lower FA compared to NABT and CONTROL in frontal and occipital WM areas. No differences were observed in MD in any brain region between NABT and CONTROL. Whereas no differences were observed in FA between NABT and CONTROL except in the occipital WM. Fibre tractography showed 31.7% to 56.1% lesser fibre tracts in LA subjects compared to CONTROL subjects. Significant differences were found between pathological tissue compared to normal appearing brain tissue and normal brain tissue. Fibre tractography exposed reduced number of neural fibres in leukoaraiosis subjects as compared to normal subjects.

**Keywords:** Diffusion tensor imaging, Diffusion tractography, Brain, Leukoaraiosis

### INTRODUCTION

The advent of advanced magnetic resonance imaging (MRI) techniques, particularly diffusion imaging has opened up new vista for more research to be done in order to understand how human brain works. Diffusion weighted imaging (DWI), which was improved to diffusion tensor imaging (DTI) is an MRI technique that detects and measures mobility of water molecules in biological cells. It has the advantages over other conventional MRI techniques in which it offers quantitative information on micromolecular and microstructural changes in biological tissues. Several parameter indices could be derived from DTI, for example, mean diffusivity (MD) and fractional anisotropy (FA). Furthermore, it also allows visualization of neural fibres through a specific technique called fibre tractography.<sup>1</sup>

Leukoaraiosis is a type of pathological condition in brain white matter which appears hyperintense on T2-weighted and fluid attenuated inversion recovery (FLAIR) MRI images.<sup>2</sup> Some studies on pathological aspects proved that leukoaraiosis is associated with age and multiple vascular risk factors such as hypertension, cerebral infarction, diabetes mellitus, as well as ischemic heart disease.<sup>3,4</sup> Besides, leukoaraiosis could also be a predictor of stroke.<sup>5</sup>

There are various reports on assessment of leukoaraiosis using diffusion imaging.<sup>6-10</sup> Nevertheless, information on comparison of DWI or DTI values between leukoaraiosis, normal appearing brain tissue, and normal brain tissue is still limited. Though there are studies reporting such information, however the region of interest (ROI) varied across different studies, as depicted in Table 1.<sup>10-14</sup> Furthermore, the parameters used in acquisition of the data images were varying. Whereas to start the study on leukoaraiosis, it is imperative to have a general view on the range of DTI values of both normal and abnormal white matter tissues provided by the MRI system.

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**Table 1** Some studies comparing DWI/ DTI values of leukoaraiosis, normal appearing brain tissue, and normal brain tissue.

Reference	MRI system, technique	ROI	Main findings related to changes of DWI/DTI values of leukoaraiosis, normal appearing brain tissue, or normal brain tissue
Helenius et al., 2002 <sup>10</sup>	Siemens 1.5 T, DWI	periventricular and deep leukoaraiosis area, frontal and occipital NAWM <sup>a</sup>	<ul style="list-style-type: none"> <li>• ADC value increased with severity of leukoaraiosis.</li> <li>• ADC value of leukoaraiosis was higher than that of ischemic stroke at hyperacute, acute, and subacute phase, similar with that of 1 month old ischemic stroke, and lower than 3 months old infarcts.</li> </ul>
O'Sullivan et al., 2001 <sup>11</sup>	GE 1.5 T, DTI	leukoaraiosis and NAWM at centrum semiovale, and anterior and posterior periventricular WM <sup>b</sup>	<ul style="list-style-type: none"> <li>• Increase of MD and reduced FA of NAWM was found in subjects with ischemic leukoaraiosis compared to normal subject.</li> <li>• The changes were observed in anterior periventricular WM and centrum semiovale. No changes were found in posterior periventricular region.</li> </ul>
Schmierer et al., 2004 <sup>12</sup>	Siemens 1.5 T, DWI	bilateral thalamus and frontal, occipital, parietal, and cerebellar NAWM	<ul style="list-style-type: none"> <li>• Patients with PPMS<sup>c</sup> showed an increase in ADC value in NAWM within 12 months compared to normal subjects.</li> <li>• ADC in frontal NAWM was associated with disability.</li> </ul>
Chabriat et al., 1999 <sup>13</sup>	GE 1.5 T, DTI	leukoaraiosis and NAWM area at centrum semiovale	<ul style="list-style-type: none"> <li>• 60% increase of water MD and parallel loss of anisotropy found in leukoaraiosis.</li> <li>• Same pattern of diffusion changes but of lesser amount was found in NAWM.</li> <li>• In patients with severe clinical status, changes in MD exceeded 70% compared with normal subjects.</li> </ul>
Uh et al., 2010 <sup>14</sup>	Phillips 3.0 T, DTI	entire leukoaraiosis and NAWM area	<ul style="list-style-type: none"> <li>• No correlations were found between CBF<sup>d</sup>, MD, or FA in NAWM with leukoaraiosis volume.</li> </ul>

<sup>a</sup>NAWM: normal appearing white matter <sup>b</sup>WM: white matter <sup>c</sup>PPMS: primary progressive multiple sclerosis <sup>d</sup>CBF: cerebral blood flow

Therefore, in this study, MD and FA were measured at various white matter, grey matter, and cerebrospinal fluid (CSF) region. Then, comparison of the DTI values was made between leukoaraiosis tissue with that of normal appearing brain tissue measured from the same leukoaraiosis subjects as well as with that of normal brain tissue measured from healthy control subjects.

## MATERIALS AND METHODS

### Subjects

Subjects were divided into two groups as described in Table 2. First group consisted of 30 subjects with leukoaraiosis who were at age below 60 years old. They were selected from 51 subjects with leukoaraiosis volunteering in other research on tocotrienol vitamin E<sup>15</sup>. They have underwent MRI scan and confirmed by a senior consultant radiologist as having leukoaraiosis in the brain. The second group consisted of 12 subjects without leukoaraiosis which were regarded as control group. Subjects without leukoaraiosis were also chosen from those at age below 60 years old.

They filled up a health screening form before participating in the study. All subjects did not present neurological and/or cardiovascular illnesses. Subjects signed an informed consent form in compliance with the regulations of Universiti Sains Malaysia ethics committee.

**Table 2** Demographic data of participating subjects.

Subjects	n <sup>a</sup>	Gender	Age (mean ± SD) (range)
With LA <sup>b</sup>	30		
LA detected at center slice			
LA at both frontal and occipital WM <sup>c</sup>	5	Male: 9	51.0 ± 5.6
LA at frontal WM only <sup>c</sup>	4	Female: 21	(39.0 - 59.2)
LA at occipital WM only <sup>c</sup>	16		
LA detected at other slices only	5		
Without LA	12	Male: 6 Female: 6	37.3 ± 11.6 (26.0 - 56.6)

<sup>a</sup>Number of subjects <sup>b</sup>LA: leukoaraiosis.

<sup>c</sup>Subjects also had LA at other image slices and areas

## MR imaging

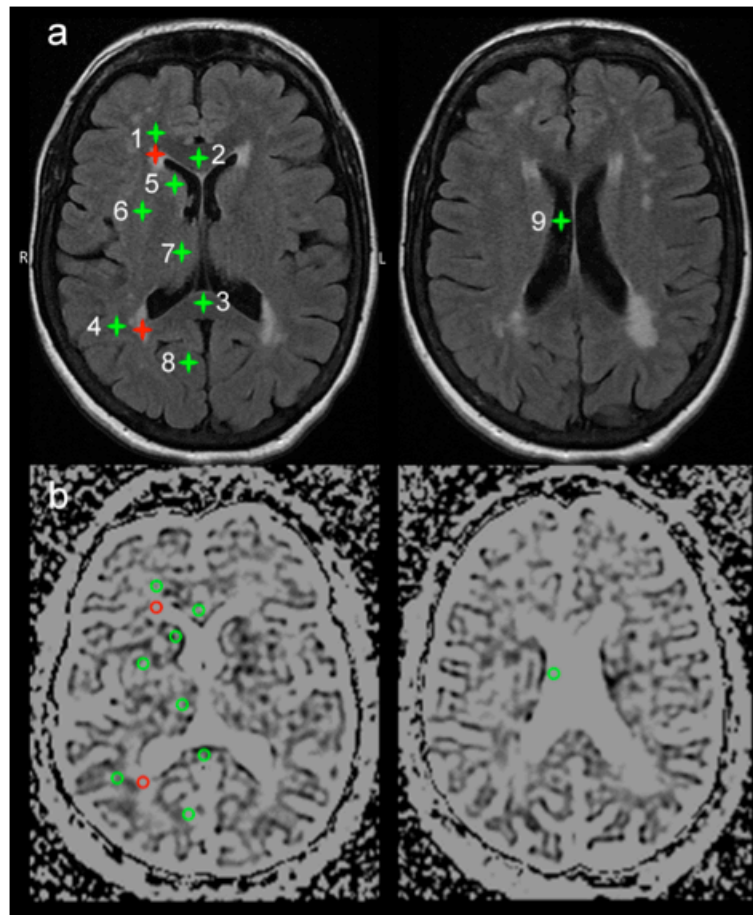
All DTI data were acquired using 1.5 Tesla MRI System (Signa HDxt, GE Healthcare). An eight-channel quadrature neurovascular array coil was utilized in the study. Data images were obtained using Stejskal-Tanner sequence with single-shot echo-planar imaging and the following protocols: TR/TE = 13 000/90.1 ms, b-value = 0 and 700 s/mm<sup>2</sup>, no. of diffusion encoding directions = 30 with 3 sets of unweighted images, axial slices parallel to the anterior – posterior commissure (AC – PC) line was obtained covering the whole brain, and without signal averaging. 2.5 × 2.5 × 2.5 mm<sup>3</sup> isotropic voxel resolution was acquired via slice thickness = 2.5 mm with no interslice gap, matrix size = 96 × 96 (zero-filled and reconstructed to 256 × 256), and FOV = 240 mm × 240 mm. All data images were sent to an independent workstation for post processing and further analysis.

## Image processing and fibre tracking

Post processing and analysis was carried out using Osirix software version 4.1.2.<sup>16</sup> Diffusion tensor elements and anisotropy at each voxel were computed. MD, FA, and color-coded FA maps were constructed. Fibre tractography was performed using commercial software, NordiICE Version 2.3.9 (NordicNeuroLab). Fiber tracking was initiated by drawing seed ROI manually on sagittal images of colour-coded FA map. Fiber tracking was performed using FA threshold of 0.1 and maximum turning angle of 30°.

## Region of interest and quantitative measurements

During region of interests (ROI) placement, ROIs were identified on the FLAIR images and simultaneously coordinated on the MD map. ROIs were drawn on the MD maps. All ROIs drawn on the MD maps were copied to the FA maps. Then, MD and FA values were measured in respective maps of all subjects. ROIs were located on the center, axial slice at the horizontal level of the striatum containing the genu and splenium of the corpus callosum. Single circular ROI with area of 0.30 ± 0.02 cm<sup>2</sup> was drawn manually in right hemisphere of the brain in white matter and grey matter areas as illustrated in Fig. 1.



**Figure 1.** An example of ROIs placement on subjects with leukoaraiosis. ROIs were identified on FLAIR image (a). Measurement of parameter indices was performed on the corresponding location on MD map (b). Red ROI represents LA, while NABT ROIs are shown in green.

As shown in Fig. 1, the anatomic locations in white matter areas are 1) frontal white matter (fWM), 2) genu, 3) splenium (Sp), and 4) occipital white matter (oWM), whereas those in grey matter areas are 5) caudate nucleus (cNuc), 6) lentiform nucleus (lNuc), 7) thalamus (Thal), and 8) occipital grey matter (oGM). ROIs were also located in 9) CSF region at another different slice containing the body of lateral ventricles. For comparison purposes, ROIs were located in similar regions according to reported studies.<sup>17,18</sup>

For subjects with leukoaraiosis, first ROI was drawn in the leukoaraiosis area (labelled as LA) while second ROI was placed on normal appearing white matter area [labelled as normal appearing brain tissue (NABT)] in similar region and slice. The NABT ROIs were carefully placed with distance at least 5 pixels from the lesion boundary to avoid mixed region of normal appearing brain tissue with leukoaraiosis tissue. All ROIs drawn at other white matter, grey matter, and CSF areas in subjects with leukoaraiosis were labelled as NABT. Whereas data measured from normal healthy subjects were labelled as CONTROL. There were altogether three sets of data namely LA, NABT, and CONTROL (Table 2 and Fig. 1).

For fibre tractography, corpus callosum, which is the largest fibre bundle in human brain was chosen for visualization of fibre tracts. Observation was made on three main fibre bundles that radiate from the corpus callosum specifically the anterior callosal fibres (ACF), posterior callosal fibres (PCF), and superior callosal fibres (SCF).<sup>19</sup> In this study, one-to-one comparison of fibre tractography was made. Therefore only two subjects either with and without leukoaraiosis were chosen. Both subjects were at similar age group (leukoaraiosis subject: 54.0 years old; control subject: 56.6 years old).

### Statistical analysis

For both MD and FA datasets statistical comparisons between LA and CONTROL were performed using independent 2-tailed Student *t* test for brain regions without LA. Brain regions with presence of LA were compared to the corresponding NABT and CONTROL using 1-way ANOVA, followed by adjusted Tukey post hoc test. For all comparisons,  $p < .05$  was considered statistically significant.

## RESULTS

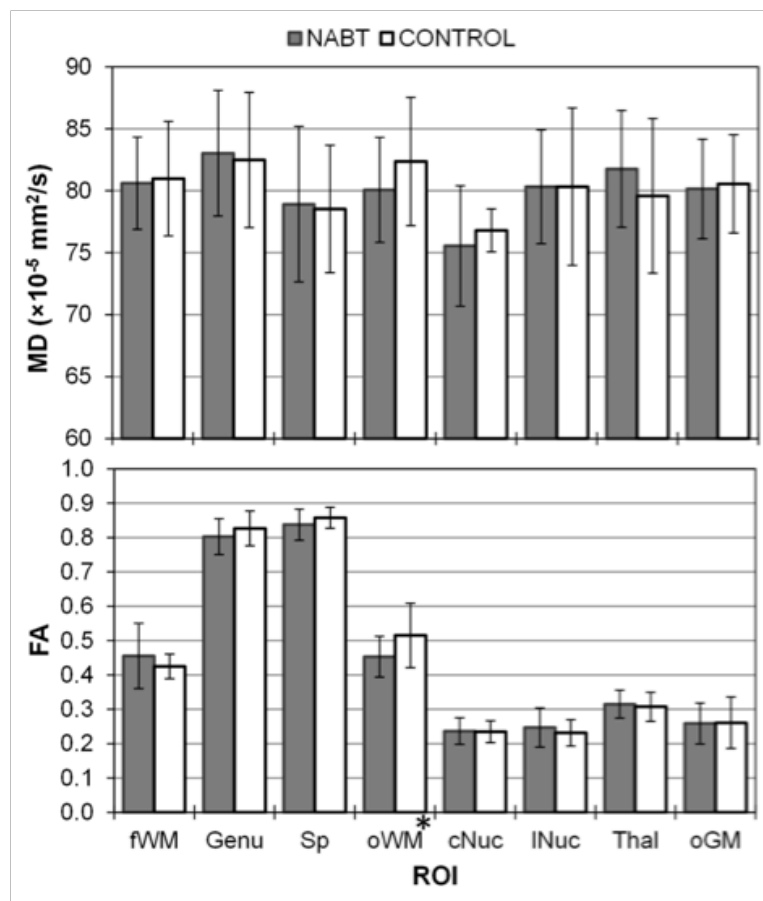
### Comparison of MD and FA between LA, NABT, and CONTROL

LA exhibited a significantly higher MD and reduced FA compared to NABT and CONTROL in both frontal and occipital areas (Table 3). Figure 2 depicts MD and FA values measured in all brain areas considered. There was no significant difference in MD values between NABT and CONTROL in all areas, including CSF. A significantly different FA value between NABT and CONTROL was only found in the occipital area. Whereas FA value of CONTROL at occipital area was observed significantly higher than that at frontal area. MD and FA exhibited by NABT at CSF were  $319.1 \pm 9.4 (\times 10^{-5} \text{ mm}^2\text{s}^{-1})$  and  $0.15 \pm 0.06$ , respectively while that for CONTROL were  $320.5 \pm 11.0 (\times 10^{-5} \text{ mm}^2\text{s}^{-1})$  and  $0.14 \pm 0.04$ , respectively.

**Table 3** MD and FA values of LA, NABT, and CONTROL at frontal and occipital white matter.

Categories	n <sup>a</sup>	MD ( $\times 10^{-5} \text{ mm}^2/\text{s}$ )	FA
Frontal white matter			
LA	9	<sup>b</sup> 96.68 (4.87)	<sup>b</sup> 0.34 (0.04)
NABT	9	80.61 (3.72)	0.46 (0.10)
CONTROL	12	80.98 (4.61)	0.43 (0.09)
Occipital white matter			
LA	21	<sup>b</sup> 94.39 (6.51)	<sup>b</sup> 0.38 (0.06)
NABT	21	80.07 (4.24)	<sup>c</sup> 0.45 (0.06)
CONTROL	12	82.36 (5.18)	<sup>d</sup> 0.52 (0.09)

Values represent mean (standard deviation). <sup>a</sup>Number of subjects <sup>b</sup>Significantly different from NABT and CONTROL ( $p < .01$ ) <sup>c</sup>Significantly different from occipital white matter of CONTROL ( $p < .05$ ) <sup>d</sup>Significantly different from frontal white matter of CONTROL ( $p < .01$ )

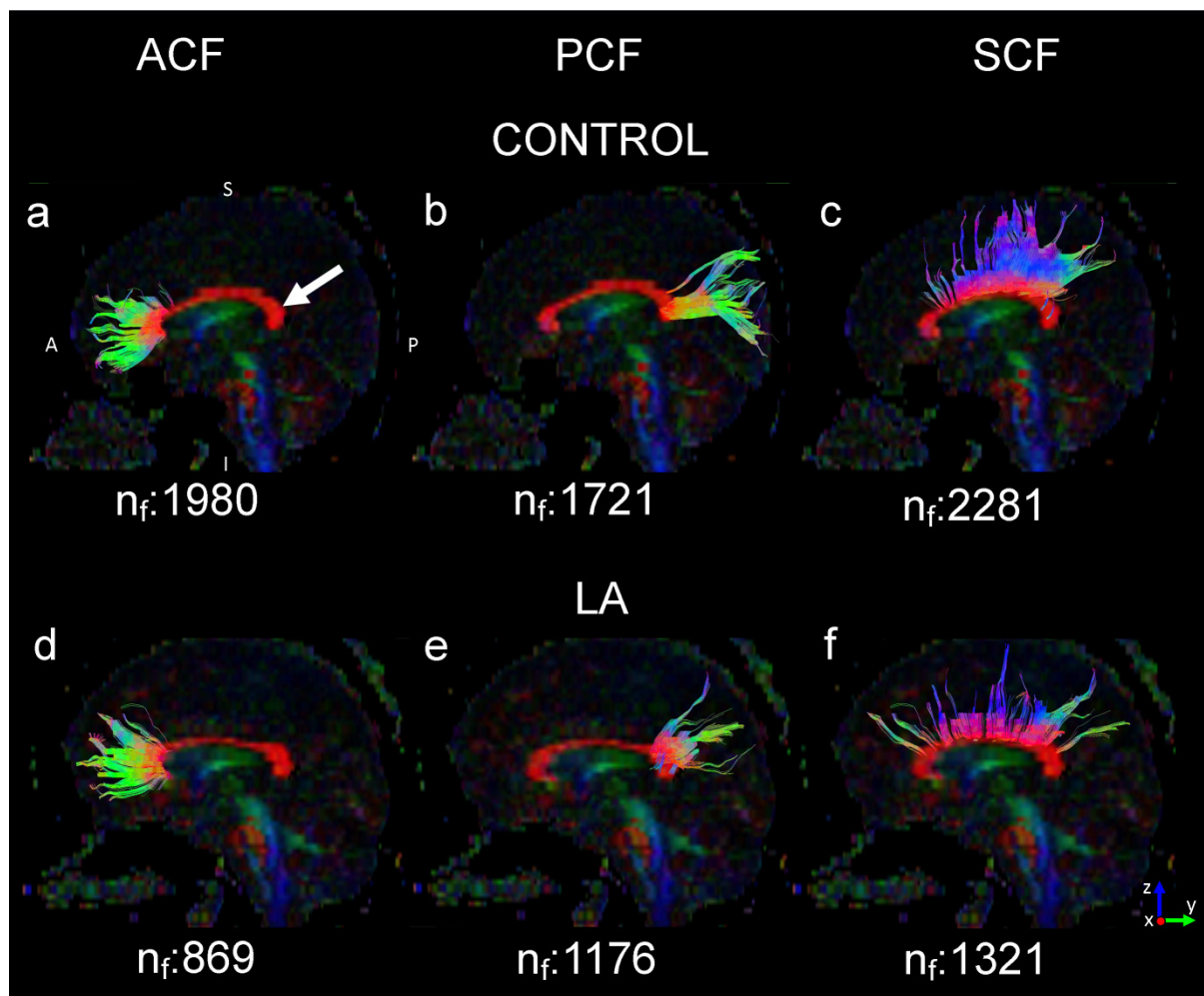


**Figure 2.** (a) MD and (b) FA values at white matter and grey matter region for NABT and CONTROL. No differences were observed in MD in any brain region between NABT and CONTROL. Whereas no differences were observed in FA between NABT and CONTROL except in the occipital WM area (indicated by asterisk).

Small variation of MD between all areas was observed ranging from 4.5% to 9.9% within NABT and from 2.3% to 10.0% within CONTROL. On the other hand, FA varied tremendously between all areas. Variation noted within NABT was from as small as 4.7% to as high as 255.1%. Meanwhile, within CONTROL, the FA values varied from 1.7% to 271.0%. For both NABT and CONTROL, genu and splenium was found exhibiting the highest FA values.

**Comparison of fibre tractography of subjects with and without leukoaraiosis**

One-to-one comparison of fibre tractography exposed major reduction in number of anterior (56.1%), posterior (31.7%), and superior (42.1%) callosal fibres in subject with LA as compared to CONTROL. The fibre tractography is depicted in Fig. 3. As shown in Fig. 3, number of fibres (n<sub>i</sub>) of the callosal fibres are as displayed. Colour indicates fibre direction as follows; red: right-left, green: anterior-posterior, and blue: superior-inferior.



**Figure 3.** Fibre tractography obtained from two subjects exhibiting the corpus callosum (red anatomy pointed by arrow) from left sagittal view. Shown are the anterior [(a) and (d)], posterior [(b) and (e)], and superior [(c) and (f)] callosal fibres.

### DISCUSSIONS

The present study was aimed at quantitatively assessing the integrity of brain white matter tissue in adults with leukoaraiosis, by comparing MD and FA values of LA and NABT areas within subjects and healthy controls. Furthermore, the investigation included also grey matter and CSF.

Comparison of MD and FA values between the three sets of data (Table 3) are shown. LA was expected to show significantly higher MD and lower FA compared to NABT and CONTROL as reported in various previous studies.<sup>10,20,21</sup> Major pathological findings that explain these results include degradation of myelin sheath of the nerve fibres,<sup>22,23</sup> enlargement of perivascular spaces,<sup>24</sup> and axonal loss<sup>2,25,26</sup> that permits the water molecules in leukoaraiotic tissues to diffuse with less restrictions. Moreover, the water molecules move in a less orderly manner in respect to specific directions, thus demonstrating a reduced FA value.

It was also found that MD values of NABT and CONTROL in all areas were not significantly different, which is in contrast with findings from previously reported studies.<sup>10-12</sup> However, the FA values of NABT were found significantly lower from that of CONTROL only in the occipital WM which may denote an early signs of tissue damage. Although the corresponding area appeared normal in the FLAIR images, it is suspected that the white matter tissue have started to deteriorate as could be detected via quantitative measurement using DTI.

In this study, MD values of white matter areas were found in range of 78.92 - 83.03 ( $\times 10^{-5}$  mm<sup>2</sup>/s) and 78.54 - 82.64 ( $\times 10^{-5}$  mm<sup>2</sup>/s) for NABT and CONTROL, respectively. While the FA values ranged from 0.45 - 0.84 for NABT and 0.43 - 0.86 for CONTROL. It was also found that MD values of grey matter areas range from 75.55 - 81.77 ( $\times 10^{-5}$  mm<sup>2</sup>/s) and 76.80 - 80.56 ( $\times 10^{-5}$  mm<sup>2</sup>/s) for NABT and CONTROL, respectively. The FA values were found ranging from 0.24 - 0.32 for NABT and 0.23 - 0.31 for CONTROL. These findings agree well with results obtained from

previous studies using similar 1.5 T MRI system, in which Ding et al. reported MD values ranged between 69.57 to 82.64 ( $\times 10^{-5}$  mm<sup>2</sup>/s) and 70.9 - 83.79 ( $\times 10^{-5}$  mm<sup>2</sup>/s) for white matter and grey matter, respectively. They also reported FA values which range from 0.42 - 0.79 for white matter and 0.11 - 0.33 for grey matter<sup>17</sup>. Besides that, findings from this study also agree with that of obtained by other previous study which reported the MD value of white matter in range of 74.20 - 89.70 ( $\times 10^{-5}$  mm<sup>2</sup>/s) and 73.00  $\times 10^{-5}$  mm<sup>2</sup>/s for grey matter.<sup>27</sup> Hunsche et al. also reported FA values between 0.44 - 0.79 for white matter and 0.37 for grey matter.

In this study, we also noticed that in CONTROL subjects, despite having similar MD at frontal and occipital white matter areas, the FA values for both areas was found to differ significantly. However, our findings were comparable with those reported in other studies on normal brain in which a higher FA was found in the occipital white matter compared to that in frontal white matter.<sup>17,28</sup> Possible reason that could explain this outcome is the ROIs at occipital white matter were placed at area with single parallel direction, specifically optic radiation fibre bundles. Higher FA shown for this area represents water molecules inside the fibres tend to move in the predominant direction, which is along the tracts, thus producing higher FA values compared to that in the frontal white matter.<sup>29</sup>

Similarly in previous studies,<sup>17,27</sup> the present study also showed high FA in the genu and splenium of the corpus callosum. This is due to its known fibre architecture which is very dense and having single, straight, and parallel direction.<sup>30</sup> Therefore, likewise in the optic radiation fibre bundles, very high FA was produced as a consequence of the water molecules inside the fibres move along the principle direction of the tracts. Great variation in FA between all areas are due to different fibres architecture in each region, in which ROIs placed in area with crossing fibres exhibits rather low FA compared to area containing fibres aligned in single direction.<sup>31</sup>

We presented fibre tractography as supplement in analysis of the brain tissues to get impression on condition of the white matter with and without leukoaraiosis. Fibre tractography showed major reduction of number of fibres in LA as compared to CONTROL which corresponds with the significant difference of MD and FA values between LA and CONTROL at frontal and occipital white matter as described earlier in this study.

There are some limitations of the study. First, the healthy subjects without leukoaraiosis are not completely age- and sex- matched as it is difficult to obtain healthy subjects without leukoaraiosis in similar age group. Though they were not in absolutely similar age group, it was reported that there were no significant difference of apparent diffusion coefficient (ADC) of normal adult brain at age below 60,<sup>32,33</sup> thus the comparison made between the two groups is reputed to be valid. Second, number of tracked fibres as well as direction and connectivity of each tracked fibre depends on the postprocessing software used. Different software might be using different fibre reconstruction method hence different reconstruction algorithm. Fibre reconstruction method itself could be classified into two broad categories that are deterministic and probabilistic.<sup>34,35</sup> Furthermore, number of tracked fibres also depends on the minimum FA index and maximum turning angle set during the analysis. Hence use of different postprocessing software or similar software with different fibre tracking parameters for analysis of the same datasets may produce different number of tracked fibres.

## CONCLUSION

By comparing MD and FA values between LA, NABT, and CONTROL, it was found that LA exhibited a significantly higher MD and lower FA as compared to NABT and CONTROL in the frontal and occipital white matter areas. No differences were found in MD in all white matter and grey matter areas between NABT and CONTROL. Whereas no differences were observed in FA between NABT and CONTROL except in the occipital white matter. Fibre tractography exposed major reduction in the number of neural fibres in leukoaraiosis subject as compared to normal subject.

## ACKNOWLEDGEMENT

The authors would like to thank Prof. Dr. Yuen Kah Hay from School of Pharmaceutical Sciences Universiti Sains Malaysia (USM). Thanks are also due to the radiographers, Mr. Mohammad Haniff Mohd Rasli, Mrs. Noor Faizura Zainal, and all staff of Imaging Unit, Advanced Medical and Dental Institute USM for their kind helps in acquiring all the data. Nur Hartini thanks Dr. Muhammad Nur Salihin Yusoff for the constructive discussion about this work. The study was funded by USM under Research University Postgraduate Research Grant Scheme (1001/PPSP/8145002).



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